UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,803	01/14/2004	James McSwiggen	SIR-MIS-00001-US-CIP[4]	5421

79693 7590 10/21/2010

Merck
c/o Sima Therapeutics, Inc.
1700 Owens Street
4th Floor
San Francisco, CA 94158

EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
10/21/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

eva_santana@merck.com
marilyn_moy@merck.com
catherine_naughton@merck.com

Office Action Summary	Application No.	Applicant(s)	
	10/757,803	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	AMY BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-20 and 33-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-20 and 33-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 8/16/10 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 5/17/10 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 18-20 and 33-49 are pending in the application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-20 and 33-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al. (The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888), in view of Matulic-Adamic et al. (US 5,998,203), Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000), and Crooke (US 5,898,031), for the reasons of record and as explained below.

It is noted that the references are of record and cited on the PTO-892 mailed on 12/21/06.

The invention of the above claims is drawn to a chemically modified double stranded nucleic acid comprising a sense strand and an antisense strand, wherein each strand is 18 to 27 nucleotides in length, 18 to 23 nucleotides of each strand are complementary to each other, and at least 18 nucleotides of the antisense strand are complementary to a target RNA sequence, and the sense strand comprises a terminal cap moiety at the 5' and 3' end. The invention is further drawn to specific terminal cap

moieties, as well as modifications to the duplex and a composition comprising the double stranded nucleic acid and a pharmaceutically acceptable carrier or diluent.

Elbashir et al. (EMBO) teach siRNAs, wherein each strand is 21-23 nucleotides in length and wherein at least 19 nucleotides of the sense strand are complementary to the antisense strand. Elbashir et al. teach chemical modification with 2'-deoxy or 2'-O-methyl modifications. Elbashir et al. teach modification of 19% of the nucleotides of a duplex 21 nucleotides in length with 2'-deoxy modifications.

Elbashir et al. teach duplexes with 2 nt 3' overhangs, as well as blunt ended duplexes wherein all 21 nucleotides are complementary between the sense and antisense strand. Elbashir et al. teach that duplexes 21 nucleotides in length with 2 nt 3' overhangs were the most efficient triggers of sequence-specific mRNA degradation. Elbashir et al. teach duplexes wherein the sense and antisense strands are complementary at 19 or 21 nucleotide positions (see for example, Figure 1D (1^{st} duplex) and Figure 1F (1^{st} duplex)). Elbashir et al. teach 2'-deoxythymidine in the 3' overhang (see page 6884). The 100% modified duplex taught by Elbashir et al. is considered to not comprise ribonucleotides.

Elbashir et al. do not teach double stranded nucleic acid molecules comprising the instantly recited terminal cap moieties and do not teach 2'-deoxy-2'-fluoro or phosphorothioate modifications. Elbashir et al. do not teach a composition comprising the double stranded nucleic acid molecule and a pharmaceutically acceptable carrier.

Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures. The enzymatic RNA molecules of Matulic-Adamic et al. are taught to be

targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3' phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example). For example, figure 3 contains a ribozyme structure that encompasses modification of at least 20%, at least 30%, at least 40% or at least 50% of the nucleotide positions, as well as the modifications instantly claimed. The modifications can be in one or both of the strands and can be modifications of different types within the same structure.

Matulic-Adamic et al. teach that preferred caps include 4', 5'-methylene nucleotides, 1-(beta-D-erythrofuranosyl) nucleotides, 4'-thio nucleotides, 1,5-anhydrohexitol nucleotides, L-nucleotides, threo-pentofuranosyl nucleotides, acyclic 3', 4'-seco nucleotides, 3,4-dihydroxybutyl nucleotides, 3,5-dihydroxypentyl nucleotides, 3'-3'-inverted nucleotide moieties, 3'-3'-inverted abasic moieties, 3'-2'-inverted nucleotide moieties, 3'-2'-inverted abasic moieties, 5'-5'-inverted nucleotide moieties, and 5'-5'-

inverted abasic moieties (see columns 3 and 4, for example). Matulic-Adamic et al. teach compositions comprising the nucleic acid and reaction buffer, which is a diluent.

Parrish et al. teach a chemically synthesized siRNA molecule, wherein each strand is 26 bp in length. Additionally, Parrish et al. teach a 742 nt long dsRNA with extensive modification with 2'-deoxy-2'-fluoro modifications, which resulted in successful RNA interference. Parrish teaches that the 2'-deoxy-2'-fluoro modifications incorporated into the long dsRNA produces unc-22 interference and furthermore described the interference as strong (+++, see figure 5).

Crooke teaches gapmer oligonucleotide chemistry and teaches that gapmer strategies increase oligonucleotide affinity to the target RNA (see column 9, for example). Crooke teaches chemical modifications that are incorporated to improve pharmacokinetic binding, absorption, distribution or clearance properties of the compound, affinity or specificity of the compound to target RNA, or modification of the charge of the compound (see column 7, for example).

Crooke teach that a particularly useful 2'-substituent group for increasing the binding affinity is the 2'-fluoro group (see column 12). Crooke also teaches 2'-O-methyl modifications.

It would have been obvious to synthesize a double stranded nucleic acid molecule with the structural characteristics taught by Elbashir et al., wherein the molecule is formulated in a composition with a diluent, as taught by Matulic-Adamic et al. It would have been obvious to incorporate the specific modifications taught by Parrish et al. and Matulic-Adamic et al.

One would have been motivated to synthesize a double stranded nucleic acid molecule, as taught by Elbashir et al. (EMBO), wherein the molecule is formulated in a composition with a diluent, because Matulic-Adamic et al. teach successful inhibition of target gene expression with nucleic acid molecules formulated in a diluent. Furthermore, the reactions performed by Elbashir et al. require diluents such as buffers and water.

One would have been motivated to synthesize a double stranded nucleic acid molecule, as taught by Elbashir et al. (EMBO), with the modifications taught by Parrish et al. and Matulic-Adamic et al. because each of the modifications were known in the art to protect nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules, as taught by Matulic-Adamic et al. Additionally, Parrish et al. and Matulic-Adamic et al. teach extensive chemical modification of long dsRNA and ribozymes, respectively, with successful inhibition of target gene expression.

Since Elbashir et al. (EMBO), Matulic-Adamic et al., and Parrish et al. teach modified double stranded nucleic acid molecules that inhibit target gene expression, and Crooke teaches gapmer oligonucleotide chemistry to improve pharmacokinetic properties of the oligonucleotide, one would have been motivated to synthesize duplexes, as taught by Elbashir et al., with each of the instantly recited modifications, as taught by Elbashir et al., Matulic-Adamic et al., and Parrish et al. in order to optimize the activity of the molecule, as taught by Crooke.

Additionally, antisense oligonucleotides, ribozymes, and dsRNAs are each commonly used for sequence-specific mRNA knockdown and each of these encounters delivery problems for effective application. Therefore, one would have been motivated to utilize the same modifications and techniques that have been utilized to overcome these problems with antisense oligonucleotides or ribozymes with siRNAs to add the same benefits to RNAi technology.

For example, Crooke teaches that gapmer oligonucleotide chemistry has provided antisense oligonucleotides with increased target affinity and pharmacokinetic properties. Crooke teaches that different modifications at different regions of the oligonucleotide have been tested in order to optimize oligonucleotide activity. Crooke teaches stepwise experimentation of modifications throughout oligonucleotides in order to find the optimal configuration. Crooke is relied upon as evidence that it is common to experiment with different known modifications at different locations to optimize oligonucleotide activity.

It would have been prima facie obvious to perform routine optimization to determine which of the known modifications or combinations of modifications are optimal. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of the specific modifications used were other than routine, that the products resulting from the optimization have any unexpected properties, or that

the results should be considered unexpected in any way as compared to the closest prior art.

Therefore, one would have been motivated to apply such a method to incorporate known modifications at various locations (i.e. regions/positions of duplex or pyrimidine v. purine) and amounts, as taught by Crooke, into the siRNA duplexes that were synthesized by Elbashir et al.

Finally, one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to antisense oligonucleotides, ribozymes, dsRNAs or siRNA duplexes, as evidenced by Elbashir et al., Matulic-Adamic et al., Parrish et al. and Crooke, wherein each of the molecules face the same challenges, and each of which can be improved with modifications. Since Crooke teaches effectively walking modifications across antisense oligonucleotides to optimize the location of the modifications and activity of the oligonucleotide and Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach successfully synthesizing modified double stranded nucleic acid molecules, one would reasonably expect for each of the modifications to benefit the double stranded nucleic acid molecules of Elbashir et al. as well. Furthermore, the long chemically modified dsRNA taught by Parrish et al. further demonstrate that extensively modified dsRNA molecules result in RNA interference activity. Since Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach modification of double stranded nucleic acid molecules and Crooke teaches experimentally determining optimal locations and levels of modification of antisense oligonucleotides, incorporating each of the modifications in the double

stranded nucleic acid molecules of Elbashir et al. is considered within the realm of routine optimization.

It is noted that Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity. However, regardless of the results of these specific modifications at 100% of the positions of one or both strands, Elbashir et al. did modify duplexes and published data regarding successful inhibition with some duplexes and unsuccessful inhibition with others, supporting that testing of such known chemical modifications is routine in the art. The results of Elbashir et al. are considered to offer motivation to incorporate chemical modifications at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant continues to argue the interpretation of the Elbashir et al. reference and argues that the instant claims require more extensive modification than the claims of US 7,022,828, wherein the board has already interpreted the article. However, the instant claims require a total of 10 pyrimidines of the sense and antisense strand to be modified (diminimus of the claim), which can be concentrated in the terminal regions which is consistent with the teachings of Elbashir et al., wherein the board agreed that Elbashir

et al. is silent as to data between 19% modification of the duplex and 100% modification of one or both strands.

It is noted that the interpretation of the Elbashir et al. (Tuschl) reference is argued in detail by applicant. However, the interpretation of the article has already been decided by the Board in the related appeal (Reexamination control 90/008,177, Patent 7,022,858), and the interpretation is consistent with that of the examiner in the instant rejection.

On page 27 of the decision, the board sets forth that appellant's argument that Tuschl teaches avoiding any 2'-O-methyl modifications is unpersuasive and misstates the teachings of Tuschl. A fair reading is that more extensive 2'-deoxy or 2'-O-methyl modification beyond the two nucleotide 3'-overhang reduces the ability of siRNAs to mediate RNAi. Stating that complete substitution abolished RNAi is not the same of stating that any 2'-O-methyl modification should be avoided. It is noted that when incorporating chemical modifications into nucleic acid inhibitory molecules, it is routine to balance stability and activity. Therefore, it is a matter of routine optimization to determine an acceptable balance between a reduction in activity and an increase in stability, as long as the molecule is still in fact active.

The decision also sets forth that nucleic acid molecules are known to be degraded or hydrolyzed by nucleases *in vivo* and in culture systems and thus it is routine in the art to modify nucleic acids to resist nuclease hydrolysis, and particularly to modify with modifications that were known to enhance stability. Similarly, capping as

disclosed by Matulic-Adamic et al. would be reasonably expected to sterically interfere with the active site of a nuclease (see page 25 of decision, for example).

Although applicant continues to read the passage on page 6885 of Elbashir et al. out of context, the only "more extensive" modification that could be referred to is the complete modification of one or both strands, as from a full reading of the article is the only modification that was tested outside of the 2 or 4 nucleotides on each end.

It is well recognized in the nucleic acid inhibitor art that some types and levels of modification will yield active molecules, and some will not, thus resulting in a need for routine optimization. Applicant appears to have set forth some type of guideline requiring for every embodiment tested by Elbashir et al. to have resulted in activity. However, Elbashir et al. does teach successful modification, which would motivate one of skill in the art to incorporate modifications and test different levels of modification. The same types of chemical modifications that have been used routinely in the antisense and ribozyme art have been used in the RNAi art as well and have produced active molecules when routinely optimized.

The instant claims are not directed to any specific pattern of modification that yielded an unexpected property, but rather are directed to a very broad scope of possible modifications at varying positions depending on the target sequence, given that the claims are not directed to any specific target.

Elbashir et al. in no way teaches away from the instant claims, which are not commensurate in scope with the 100% modified duplexes that were inactive of Elbashir

et al. Elbashir et al. offers motivation to incorporate modifications to reduce the cost of RNA synthesis and to enhance RNase resistance of siRNA duplexes (see page 6885, column 1). The fact that Elbashir et al. is silent as to modification between 19% and 100% (of one or both strands) would in fact motivate the skilled artisan to modify more extensively than the 19% to optimize the activity/stability balance.

Applicant argues that the review by BPAI of Elbashir that more extensive modification beyond the 8/42 positions reduced the ability to mediate RNAi is consistent with applicant's interpretation that Elbashir et al. teaches away from further modification. This conclusion is in error given that reduction in the ability to mediate RNAi still yields molecules that are active. It is widely accepted in the nucleic acid inhibitor field that a balance is needed between stability and activity and thus a reduction in activity is often accepted to gain stability, as long as the molecule is still active. The claims do not require any specific level of activity. Applicant erroneously interprets the decision by the board as consistent with a teaching away by Elbashir et al.

Applicant argues that Elbashir should have taken a different approach based upon the results of Parrish if consistent with the examiner's interpretation. However, the fact that Elbashir focused on a different approach than hypothesized by applicant is irrelevant.

Applicant argues that Parrish et al. teach away from the instant claims. The basis of such an assertion is unclear given that Parrish teaches extensive 2'-deoxy-2'-flouro uridine modification with strong RNAi activity. The 2'-deoxy-2'-flouro uridine modification represents a dsRNA that was extensively modified and acted via RNAi.

Although applicant continues to argue elements that are not claimed, applicant has not argued the fact that Parrish teaches a dsRNA with 2'-deoxy-2'-flouro uridine modification that resulted in strong activity. There is no reason to expect that shorter dsRNAs, wherein Parrish itself teaches that duplexes 26bp in length act via RNAi, would not remain active with the same modification, particularly given that the long dsRNA of Parrish was necessarily cleaved via Dicer in the cell into short siRNA molecules in order to be loaded into RISC and be active.

Applicant argues that there would not have been a reasonable expectation of success. Contrary to applicant's argument, this is not true given the instantly claimed genus. It was well within the technical grasp of the skilled artisan to combine chemical modifications that were known and routinely used to enhance stability of nucleic acid therapeutic molecules to arrive at molecules within he instantly claimed genus that would likely have activity, as it was known in the art to balance stability and activity via routinely testing different combinations/quantities of such modifications.

It is noted again that there are only two options to incorporate the instant modifications, purine or pyrimidine; wherein the quantity and location of purines or pyrimidines is entirely target sequence specific, although the instant claims are not closed to any specific target.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AMY BOWMAN
Primary Examiner
Art Unit 1635

/AMY BOWMAN/
Primary Examiner, Art Unit 1635